

Notice of Allowability	Application No.	Applicant(s)	
	09/555,139	VAN SCHARRENBURG ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 2/5/04.
2. ☒ The allowed claim(s) is/are 10-28.
3. ☒ The drawings filed on 25 May 2000 are accepted by the Examiner.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☒ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|---|--|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____. |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO-1449 or PTO/SB/08),
Paper No./Mail Date _____ | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9. <input type="checkbox"/> Other _____. |

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Jeremy Stipkala on May 3, 2004.

On page 6, line 20, please insert the following:

BRIEF DESCRIPTION OF DRAWINGS

FIGURE 1 - Observed serum IgG antibody responses against HA B/Harbin (solid bars) and HA A/Johannesburg (open bars). Control: PBS treatment; HA: antigen given alone; pLTB: antigen given together with pLTB.

FIGURE 2 - Observed serum IgG antibody responses against HA B/Harbin. NONE: antigen given alone; pLTB: antigen given together with pLTB; hLTB: antigen given together with hLTB.

FIGURE 3 - Observed nasal influenza-specific IgA antibody responses against HA B/Harbin (solid bars) and HA A/Johannesburg (open bars). Control: PBS treatment; HA: antigen given alone; pLTB: antigen given together with pLTB.

FIGURE 4 - Observed nasal HA-specific S-IgA antibody responses against HA B/Harbin. pLTB: antigen given together with pLTB; hLTB: antigen given together with hLTB.

FIGURE 5 - Observed urogenital HA-specific S-IgA antibody responses against HA B/Harbin (solid bars) and HA A/Johannesburg (open bars). Control: PBS treatment; HA: antigen given alone; pLTB: antigen given together with pLTB.

FIGURE 6 - Observed serum IgG titres on days 6, 13, 20 and 28, respectively (bars from left to right for each of the vaccination regimes). n.i.: controls treated with PBS; pLTB: HA and recombinant pLTB applied i.n.; s.c.: HA applied s.c.; conv.: convalescent mice.

FIGURE 7 - Post-challenge virus load in nose (hatched bars) and lungs (open bars). n.i.: controls treated with PBS; pLTB: HA and recombinant pLTB applied i.n.; conv.: convalescent mice; HA s.c.: HA applied s.c.

FIGURE 8 - Observed nasal (hatched bars) and vaginal (open bars) IgA antibody responses. n.i.: controls treated with PBS; pLTB: HA and recombinant pLTB applied i.n.; conv.: convalescent mice; HA s.c.: HA applied s.c.

2. The following is an examiner's statement of reasons for allowance:

The prior art does not teach or suggest a composition comprising at least one immunogen and an adjuvanting amount of B subunits of heat-labile enterotoxin of *E.coli*, wherein said B subunits are free of A subunit and toxic LT holotoxin, and wherein said at least one immunogen is in the form of aggregates, clusters, micelles, virosomes, or rosettes, or a mixture of two or more of the foregoing. The Tamura reference does not teach the use of at least one immunogen is in the form of aggregates, clusters, micelles, virosomes, or rosettes, or a mixture of two or more of the foregoing. For influenza vaccine, for example, Tamura teaches a vaccine [can be made] comprising the whole or a part of hemagglutinin (HA), . . . which [is] obtainable by purifying a virus, which is grown in embryonated eggs, with ether and detergent, or by genetic engineering techniques or chemical synthesis." Tamura, et al. col. 9, lines 1-6. Nothing within Tamura's disclosure describes aggregation or association of the antigen. In fact, the method of isolating and purifying hemagglutinin antigen employed by Tamura et al. yields "soluble HA antigen". See specification at page 3, line 20 to page 4, line 2. Tamura et al prepares the HA vaccines by treating influenza virus "with ether to remove the lipids". In addition, Tamura et al. himself concluded that his prior studies were tainted by the presence of 0.1% in Sigma's CTB. (Tamura et al. Vaccine 12(5): 419-26, 424. 1994). Accordingly, the Tamura reference also did not teach or use B subunits completely free of holotoxin. Additionally, Tamura teaches that the use of a trace of LTB, free of A subunit, lacked adjuvant activity when used in conjunction with soluble antigen. Tamura teaches that the addition of a trace amount of A subunit is necessary

to in order for the LTB subunits to exert adjuvant activity to soluble antigen. Applicants have unexpectedly found that the trace of A subunit is not necessary for the LTB subunit to exert very powerful adjuvant activity when the immunogen is in the form of aggregates, clusters, micelles, virosomes, or rosettes, or a mixture of two or more of the foregoing.

The prior art does not teach or suggest the forms of the immunogens now claimed. Each independent claim recites that the immunogen is "in the form of aggregates, clusters, micelles, virosomes, or rosettes, or a mixture of two or more of the foregoing." In addition, each independent claim states that "said at least one immunogen is not covalently coupled to said B subunits", i.e., said language excludes fusion proteins of B subunits and an immunogen. Not one of the cited documents teaches or suggests these forms of immunogen. Tamura et al., Kikuta et al., and Hirabayashi et al. all use soluble HA antigen isolated according to the method of Davenport et al., which method produces non-particulate immunogens. Hirst et al. and Fujisawa et al. both teach fusion protein immunogens, in which the immunogen is covalently bound to the B subunits. Thus, none of the cited documents teach vaccine composition comprising at least one immunogen and an adjuvanting amount of B subunits of heat-labile enterotoxin (LTB), wherein said B subunits are free of A subunit and toxic LT holotoxin, wherein said at least one immunogen that is *not* covalently bound to the B subunit, and wherein the immunogen is in the form of aggregates, clusters, micelles, virosomes, or rosettes, or a mixture of two or more of the foregoing.

Art Unit: 1645

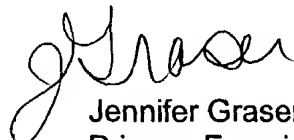
Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

2. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

 5/3/04
Jennifer Graser
Primary Examiner
Art Unit 1645